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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,083	09/12/2001	Craig A. Rosen	PS-805	9454

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EXAMINER	
SHEINBERG, MONIKA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/950,083	ROSEN ET AL.	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15 and 24-55* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15 and 24-55* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) ~~Paper No(s)/Mail Date~~ *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*.

DETAILED ACTION

Response to Amendment 16 December 2003

1. Applicants' arguments, file: 16 December 2003, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

2. The cancellation of claims 1, 8, 13, 17-20 and 22 is acknowledged.

3. Claims 15 and 24-55 are pending.

4. Claim 15 remains withdrawn.

5. Claims 24 –55 have been examined.

6. ***Note:*** It is Applicants responsibility to provide the correct page and line numbers for support when referencing the specification. Although Applicants did provide page and line number of support for arguments and amendments to the claims in the instant response (a majority of those provided were incorrect). The examiner has attempted to locate the proper pages. However, as the specification is over 4500 pages, any additional pages not found by the examiner, but deemed important for further citation by applicant, will not affect the finality of the instant office action.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 101/112

7. The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph,

"Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 24-55 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well-established utility.

9. The asserted specific utilities are based upon homology/identity to experimentally known sequences after translating the cDNA. It is noted that applicant(s) have stated in the response (filed May 7, 2003) that "Gene No. 570 is 100% identical to delta-tubulin" and that it is homologous to tubulin Uni3 [Chlamydomonas reinhardtii].

570	HDPKC55	Cardiovascular, Immune/Hematopoetic, Reproductive

10. The specification asserts that the polypeptide compounds, proteins, may be useful in a variety functional/biological activities based on a correspondence of similarity to a known protein. Table 1D indicates that in the use of the gene corresponding to SEQ ID NO: 3177

potentially "**may** be used in preventing, treating, diagnosing or ameliorating the disease(s) or disorder(s)"(p. 18, [24]). Ideally, the use of examples in a given specification typically serve to demonstrate at least the critical limitations and/or requirements in order to make/use an invention. However, the examples are generic in nature and not specific to the elected sequence. The elected sequence is identified by the specification by a variety of tables that are based solely on predictive analyses that have no experimental support. The listed diseases and disorders described by the preferred indications of the polypeptide are non-specific, but covering a wide array of diseases and disorders. The laundry list of diseases or disorders that are encompassed within the above specified indications appear to cover an extremely broad range of disorders; for example those of reproductive indications are listed from page 4367-4370 of the specification while those of cardiovascular disorders are listed from pages 4341-4343. Thus no specific use has actually been indicated as the preferred embodiment of SEQ ID NO: 3177, other than it is homologous to delta tubulin. In fact, the specification summarizes modern biotechnology generally but never connects the elected sequence to any particular or specific utility. This wishlist desire for a utility for the claimed sequence falls short of a readily available utility. The exemplary assays described within the specification are general to any disclosed polypeptide and are non-specific uses that are applicable to proteins in general and not particular or specific to the polypeptide being claimed.

11. In addition, the protein is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, the protein is not experimentally characterized in any fashion, but partially characterized by predictions based on homology analyses to public database entries. The research contemplated by applicant(s) to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities such as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the protein compound(s) such that another non-asserted utility would be well established for the compounds.

12. Claims 24-55 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by a specific, substantial, and credible utility, or, alternatively, a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Response to Arguments

13. The applicant's arguments have been fully considered and have not been found persuasive.

The current USPTO utility guidelines state (*emphasis added*):

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes chromosome markers, or forensic or diagnostic markers. Therefore the credibility of such an assertion would not be questioned, although such a use might fail the- specific and substantial tests (see below).

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. *Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.*
B. *A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. ' 10 1.)*
C. *A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility."*
D. *A method of making a material that itself has no specific, substantial, and credible utility. '*
E. *A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.*

Note that "throw away" utilities do not meet the tests for a specific or substantial utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial asserted utility would be considered to be met.

A "Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. 'Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at 2107 - 2107.02.

14. On pages 20-21, bridging paragraph of the response: Applicants assert that any utility unless proven 'false' by the examiner fulfill requirements of the utility under 35 USC 101, of which examiner has not provided sufficient evidence. This argument has been thoroughly reviewed but is not found to be persuasive because while the utilities are credible, they are not specific and not substantial. The asserted utilities do not take advantage of the specific structure, sequence, or properties of the claimed SEQ ID NO: 3177, but rather are uses common to all polypeptides. The utility of an invention must satisfy three criteria in order to be valid: the utility must be credible, specific, and substantial. Examiner is not challenging the credibility of the instant invention. The assertion that the utility of the present invention is credible (and examiner does not suggest that such uses are not credible), does not in any way affect the fact that the utility is also non-specific and not substantial. Thus the argument is found non-persuasive.

15. On page 21, 1st paragraph of the response: Applicants assert that Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility und 35 USC 101 because the Examiner failed to (a) show the asserted utility is not specific, substantial, and credible; (b) show support for factual findings relied upon; and (c) showed an evaluation of the closest prior art. This argument has been thoroughly reviewed but is not found to be persuasive

because with respect to specific, substantial and credible utility, Examiner has demonstrated the lack of specific utility (sections #9-10 above), and lack of substantial utility (section #12) (as stated above, Examiner is not challenging the credibility of the instant invention). With respect to the display of factual findings relied upon, Examiner points to specific sections of the specification as seen in section #11 (table 1D and various pages of the specification). With respect to the evaluation of the closest prior art, no prior art set forth any well established utility thus it is unclear what prior art Examiner should have cited. With respect to the delta-tubulin (accession # Q9UJT1) submitted by Applicants, the homology to delta-tubulin sequence was disclosed post-priority date (2000).

16. On page 21, 2nd paragraph to page 22, 2nd paragraph of the response: Applicants assert that because SEQ ID NO: 3177 has 100% homology to delta tubulin,

> ...it is likely to share some biological functions of tubulins. Combined with its tissue distribution in human microvascular endothelial cells, polypeptides of the claimed invention and antibodies to the claimed would be useful for the diagnosis, treatment and/or prevention of microtubule associated vascular disorders affecting endothelial tissues which include, but are not limited to atherosclerosis, arteriosclerosis and stroke. (p. 22, 2nd paragraph)

This argument has been thoroughly reviewed and not found persuasive because the art does not provide what the specific utilities of delta tubulin are, such as what the skilled artisan can do with a delta-tubulin like protein, or what diseases or disorders are specifically correlated to delta-tubulin. In addition, the art states the distinctiveness of delta-tubulin from the rest of the centrosomal proteins and tubulins in general [Chang et al, 2000, IDS; and Smrzka et al, 2000, IDS]. Chang et al teaches that delta tubulin is a 'non-microtubule tubulin' (p. 34, 1st column, 1st paragraph), which has "patterns of localization that are distinct from [epsilon-tubulin] and from all other known centrosomal proteins, including gamma-tubulin" (p. 30, 2nd column, 1st paragraph). Smrzka et al teaches that mammalian delta-tubulin has an unknown specialized role that is distinct from other known tubulins; due to localization studies, a role potentially in spermiogenesis or centrioles of somatic cells (p. 413, abstract to 2nd column, 1st paragraph). Although a different potential affects based upon potential interactions that are undefined are mentioned with the art, the specific utilities delta-tubulin are not known in the prior art or in post-filing art. Therefore a skilled artisan would not know what biological functions could be

shared with the other tubulins; what microtubule associated vascular disorders could be diagnosed (especially if delta-tubulin has been demonstrated to be a non-microtubule tubulin (Chang et al); nor how delta-tubulin would be utilized in any treatment or prevention therapy. Further, the specification does not provide or teach specifically that SEQ ID NO: 3177 corresponds to 'microtubule associated vascular disorders'. The specification (Table 1D, p. 1753) merely points to a laundry list of diseases and disorders (pp. 4306-4370) general to the cardiovascular system, the immune/hematopoetic systems, and reproductive system, of which none are specified as microtubule associated vascular disorders. Arteriosclerosis, for example is mentioned as coronary arteriosclerosis on page 4342 (paragraph 699) and cerebral arteriosclerosis is mentioned on p. 4322 (paragraph 703); however these are mentioned within a large non-specific list of over 3 pages dedicated to diseases and disorders of the cardiovascular system. With respects to tissue distribution, Table 1B (p. 538, 4th row), demonstrates that the tissue distribution is not limited to human microvascular endothelial cells (H0266:2, refer to Table 4 for cDNA library description, p. 4123)(it is to be noted that it is not indicated whether the cells are normal or diseased). The table demonstrates expression in stomach adenocarcinoma (L0662:2, p. 4145) and total fetal tissue (L0759:2, p.4147) at the same level of expression (level 2) as seen in the human microvascular endothelial cells; while further expression in for example, human prostate (H0032:1, p. 4118) and pancreas adenocarcinoma (L0659:1, p. 4145). Therefore it is unclear how a skilled artisan could make a diagnosis of anything when the tissue distribution was not specific to any tissue type or disease/disorder type. Thus if no diagnosis can occur, then how can the claimed peptide be utilized in a treatment for disease that is not specifically correlated to the claimed peptide or delta tubulin. If the skilled artisan cannot correlate a specific disease or disorder that corresponds to the claimed peptide, it is unclear how a prevention of the disease or disorder can occur. The specification does not provide any evidence that specifically correlates delta-tubulin or SEQ ID NO: 3177 to microtubule associated vascular disorders such as atherosclerosis, arteriosclerosis and/or stroke. Therefore, the specification fails to provide evidence of the specific or substantial utilities of the complete or partial sequence of SEQ ID NO: 3177, aside from being homologous structurally to delta-tubulin which also lacks disclosed specific and/or substantial utilities within the specification and prior art.

In addition the claims are not limited to the whole sequence, which has 100% homology to delta-tubulin. The claims encompass fragments and/or percent sequence similarities of SEQ ID NO: 3177. A percentage sequence similarity of less than 100 % homology and fragments including 100% homology, is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known polypeptide absent factual evidence. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. Any variation in amino acid sequence results in a new and independent sequence that does not necessarily reliably result in similar or identical biological activities as result, for example, from altered folding patterns. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. In the instant case, since the function/activity of delta-tubulin and SEQ ID NO: 3177 is unknown, the claimed sequence homologies also result in an unpredictable, thus unreliable, correspondence between the claimed fragment or variant polypeptide and the SEQ ID NO, and therefore lacks support regarding utility and enablement. For further clarification of the lack predictability, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork [Genome Research, 10: 398-400 (2000)] teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. [PNAS 92; 6743-6747 (1995)] teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. [J. Baceriol. 183 (8); 2405-2410 (2001)] teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. [Science 282: 1315-1317 (1998)] teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturases. Therefore, as stated above, any variation in amino acid sequence is largely unpredictable and results in a new and independent sequence that does not necessarily reliably result in a peptide having similar or identical biological activities when the biological activity of the peptide is known; and more specifically

in the instant case, when the function of the peptide of SEQ ID NO: 3177 and delta-tubulin are unknown.

17. On page 23, 2nd-3rd paragraph of the response: In response to Examiner's 'laundry list' argument, Applicants assert, (emphasis added)

> ... the disclosure of uses for the claimed invention does not negate the specificity of any one of those uses [... It] is common and sensible for an applicant to identify several specific utilities for an invention. [... however] the claimed invention would be useful for the diagnosis, treatment and/or prevention of microtubule-associated vascular disorders affecting endothelial tissues which include, but are not limited to, atherosclerosis, arteriosclerosis and stroke.

This argument has been thoroughly reviewed but is not found to be persuasive for reason discussed in section #17 above. As stated, nowhere in the specification are the teachings or suggestion that SEQ ID NO: 3177 be utilized in diagnosis, treatment or prevention of microtubule associated vascular disorders such as atherosclerosis, arteriosclerosis and/or stroke. Although atherosclerosis, arteriosclerosis and/or stroke may be considered a microtubule associated vascular disorder, the specification does not correlate any of these specifically to SEQ ID NO: 3177 nor delta tubulin other than being listed with a listing of diseases and disorders general to the cardiovascular system, the immune/hematopoetic systems, and reproductive system. Although Applicants have disclosed these microtubule associated vascular disorders in the specification within a multitude of other potential diseases and disorders on – i.e. immune deficiencies/disorders on pages 4306-4322 or cardiovascular disorders on pages 4341-4344 – these listed diseases and disorders are disclosed in reference to all the sequences within the specification on pages 4306-4378 in a general fashion, while nowhere in the specification is there a specific teaching or evidence to the differential expression of SEQ ID NO: 3177 being diagnostic for example of atherosclerosis, or arteriosclerosis, or stroke. In addition, post-filing art suggest that delta-tubulin is a "non-microtubule" tubulin, therefore the art does not support an association between SEQ ID NO: 3177 and microtubule associated vascular disorders.

18. On page 24, 1st-2nd paragraph of the response: Based upon the 100% homology between SEQ ID NO: 3177 and delta tubulin, Applicants assert that because "it was already believe tubulins could be used as therapeutic targets in, for instance, the treatment of atherosclerosis" as

per Chaldakov (IDS, 1982), the claimed peptide is asserted to carry the same potential utility. In addition, Applicant points to Micheletti et al. (IDS, 2003) for confirmation of targeting tubulins with a tubulin-binding agent that "induced the alteration of endothelial cell morphology and resulted in the loss of blood vessel integrity in the case of tumor treatment (1st paragraph). Applicant further provides references to support the utility of tubulins in general:

> ...recent publications identified delta-tubulin as a centrosomal tubulin, which interacts with gamma tubulin and could regulate cellular functions such as microtubule nucleation or centriole/basal body duplication. (2nd paragraph).

This argument has been thoroughly reviewed but is not found to be persuasive for reason discussed in sections #16 and 17 above. In addition, the publications provided have been thoroughly reviewed however not found to teach any specific or substantial utility for delta-tubulin or a delta-tubulin like protein such as SEQ ID NO: 3177. The interaction that 'could regulate cellular functions' does not provide any evidence that it does or if it does, at what degree and what degree of interaction would directly or indirectly result in disease. This disclosure does not provide the skilled artisan with any specific diagnosis, treatment therapy decision, or prevention steps with regard to any specific disease or disorder. The identification of the peptide's interactions and potential activity remains as intermediary steps of a process that does not result in an immediate 'real world' use that a skilled artisan could immediately apply, for example, to diagnostics. Chaldakov discusses tubulins as targets for athresclerosis in a general fashion at a time when delta-tubulin had not yet been present in the prior art. In addition, once present in the art as stated above, delta-tubulin has been shown to be distinctly different than rest of the centrosomal proteins and tubulins. Micheletti et al. demonstrates a tubulin-binding agent specific to those that affect microtubule dynamics, while in the instant case, delta-tubulin is a "non-microtubule tubulin" as taught by Chang et al. In addition, Micheletti et al. discusses tubulins in a general fashion without indication of which tubulins are affected by the tubulin-binding agent. The claimed invention provides a research tool to further characterize the protein and its biological activities, which, as noted above, are different than those of other tubulins and therefore requires unpredictable, and undue experimentation. Identifying (such as stating its homology to delta-tubulin) and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use.

19. On page 24, 2nd paragraph of the response: Applicant asserts that the claimed polypeptides can be used "in the detection or treatment of a specific disease such as atherosclerosis [which] is certainly a 'real world', substantial use"(2nd paragraph, last phrase). However the specification does not teach or suggest, how a skilled artisan would determine the detection of SEQ ID NO: 3177 to be diagnostic of atherosclerosis when SEQ ID NO: 3177 appears to be expressed in a variety of tissues both normal and diseased not limited to one system. In addition, as stated previously, nowhere in the specification is there any evidence that SEQ ID NO: 3177 or delta-tubulin are diagnostic of atherosclerosis.

20. On page 25, 1st paragraph of the response: Applicants assert that with early stage development of therapeutic inventions "includes the expectation of further research and development" (1st paragraph). This argument has been thoroughly reviewed but is not found to be persuasive for reasons as stated in section # 18, to further characterize the protein and its biological activities, which are different than those of other tubulins, would require further unpredictable and undue experimentation. As discussed above, the level of unpredictability in the art is very high both at the time of filing the instant application and within the state of the art now. Any further research and development to study the function or efficacy of the instant claimed peptide, that although has a disclosed structure but does not have a known function, is not considered a "real world" context of use.

21. On page 25, 2nd paragraph of the response: Applicants assert that "homology-based assertions of utilities are not *per se* implausible [...and...] Applicants point out that the asserted utilities for Gene NO. 250 of the present invention are based on perfect sequence homology" (2nd paragraph). This argument has been thoroughly reviewed but is not found to be persuasive for reasons discussed in sections # 17 and 19. [Examiner would like to note that it is Gene NO. 570 and not Gene NO. 250, that correlates to the elected sequence SEQ ID NO: 3177; the response to the argument is under the assumption that the referenced gene number was intended to be Gene No. 570]. In addition, not all the claims are directed to peptide sequences of *perfect* sequence homology, see claims 36-45.

22. Therefore, the arguments are non-persuasive to overcome the rejection.

23. The rejection of claims 24, 25, 27-30, 31 and 33-45 is maintained and reiterated under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

24. WRITTEN DESCRIPTION: Claims 24, 25, 27-30, 31 and 33-45 are directed to a predicted polypeptide sequence. The claims are directed to encompass proteins corresponding to sequences of 90% or 95% identity to the overall of SEQ ID NO: 3177. The specific 10% or 5% that are not identical to the elected sequence are represented by the claim are not supported by the specification. Although the sequence itself distinguishes the structural features of the amino [corrected typo, previously 'nucleic'] acid sequence, beyond exact identity (be it in entirety or to contiguous fragments) of the elected SEQ ID NO: 3177, are included but not disclosed as to written description. Each variation of the 5% or 10% non-identical, results in a new and independent sequence that does not reliably result in similar or identical biological activities as a result, for example, from altered folding patterns. For example, it is known that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. Absent factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. Thus the instant claims are directed to encompass peptide sequences that correspond to sequences from other species, mutated fragment sequences, allelic variants, splice variants, and so forth. None of these additional sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Response to Arguments

25. On page 27, 2nd paragraph of the response: Applicants assert that "while applicant must 'blaze marks on trees,' rather than 'simply [provide] the public with a forest of tress,' an Applicant is not required to explicitly describe each of the trees in the forest" [in citing *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1227 (Fed. Cir. 2000)]. This argument has been thoroughly reviewed but is not found to be persuasive because the specification does not reflect possession of mutants, variants, or homologs of SEQ IDNO: 3177 from any source by merely disclosing the sequence of SEQ ID NO: 3177 and general descriptions on how to alter it. For example, isolation of SEQ ID NO: 3177 from the deposit HDPKC55 does not reflect possession of mutants or variants of SEQ ID NO: 3177, nor possession of peptides of any magnitude and/or content. For further clarification, sequences encompassed are of any magnitude and/or content that comprise at least the specified region of SEQ ID NO: 3177 are included in the above: as seen in claim 24, for example, "an isolated protein *comprising* amino acid residues 29-453 of SEQ ID NO: 3177." Flanking amino acids are included within the mutations of an amino acid sequence that can alter the folding pattern. While one of skill in the art could argue that the claimed genus of polypeptides is adequately described since one can isolate these peptide sequences using the polypeptide/polynucleotide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork [Genome Research, 10: 398-400 (2000)] teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. [PNAS 92; 6743-6747 (1995)] teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. [J. Baceriol. 183 (8); 2405-2410 (2001)] teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. [Science 282: 1315-1317 (1998)] teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturases. The genus of peptides comprised by the claim is a large variable genus, which can potentially encode proteins of diverse functions. The specification only discloses a single

species of the genus, i.e. the polypeptide of SEQ ID NO: 3177, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

With the exception of a substantially purified amino acid molecule consisting of the sequence of SEQ ID NO: 3177, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997);
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> *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

26. On page 28, 3rd paragraph of the response: Applicants argue that applicants were in possession of the polypeptides encompassed by the claims because the polynucleotides encoding the claims polypeptides were submitted within deposit HDPKC55, while the specification described how to isolate said polypeptide. Further, that

> Nothing more than a basic knowledge of the genetic code and what is described in the specification would be required for the skilled artisan to identify every single one of the polypeptides that are 90% or 95% identical to the amino acid sequence of SEQ ID NO: 3177. Clearly, such knowledge is well within what is expected of the skilled artisan. (3rd paragraph).

This argument has been thoroughly reviewed but is not found to be persuasive because of reasons stated above in section # 25. As discussed, any variation in amino acid sequence results in a new and independent sequence that does not reliably result in similar or identical biological activities as result for example from altered folding patterns. The claims remain encompassing sequences that are not described by the specification.

27. On page 29, 2nd-3rd paragraph of the response: Applicants further assert that "the claimed invention is specifically directed to human secreted proteins (*see*, Abstract), and in particular, polypeptides corresponding to the selected clone of the invention HDPKC55 (3rd paragraph). This arguments has been thoroughly reviewed yet is not found persuasive because this limitation is not within the claims. Further, even if they were, the specification has not taught what distinguishes a "human" variant or fragment of SEQ ID NO:3177 from a variant or fragment from another species.

28. On page 29, 3rd paragraph of the response: Applicants assert that the disclosure provides adequate written description support for the mutated fragment sequences, allelic variants sequences or splice variants because "Applicants have provided the core structural feature of the polypeptides of the inventions, namely SEQ ID NO: 3177" (3rd paragraph). This argument has been thoroughly reviewed but is not found to be persuasive because of reasons stated above in section # 25.

Specification Objections

The objection to the specification is maintained and reiterated because it continues to contain embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code in the specification as in the following place for example, p. 2404, paragraph [202]. Applicants are requested to ensure that embedded hyperlinks and/or other form of browser-executable code are removed from elsewhere in the specification as well. See MPEP § 608.01.

Conclusion

MAINTAINED

- Claims 24-55 are rejected under 35 U.S.C. § 101/112 – utility.
- Claims 24, 25, 27-30, 31 and 33-45 are rejected under 35 U.S.C. 112, first paragraph – written description.
- Specification objection.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The central **Fax number is (703) 872-9306.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (571) 272-0749. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Sitton, can be reached at (571) 272-0752. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (571) 272-0518, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

March 9, 2004
Monika B. Sheinberg
Art Unit 1634

JEHANNE SITTON
PRIMARY EXAMINER
3/9/04